REMARKS

Claims 2-5, 7-10, 12-42, 46, 53, 55-58, 61-74, 77-96, 98-108, 110-118, 121-123, 129-150, 154-156, 158-160, 171-177, 183, 185, 187, 189, 190, 197, 198 and 200-202 are withdrawn from this application. Claims 127, 128, 152, 153, 178-182, 186, 188, 192-196, 199 and 203-204 were previously cancelled. Applicants reserve the right to file continuation or divisional applications directed to the cancelled or withdrawn subject matter. Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are currently pending.

Objections to the Drawings

The Examiner has objected to the drawings as containing informalities. Applicants respectfully request clarification of the objection. Formal drawings were submitted on January 28, 2004. A replacement Figure 1 was submitted on May 26, 2005. An examination of the submitted documents as they appear on the U.S. Patent and Trademark Office PAIR system shows none of the defects described by the Examiner. Figures 16 and 17 clearly show the effect of Glucocerbroside on spleen and liver CD4/CD8 ratio. These figures are not blank. The X axis of Figure 6 is clearly labeled as "IL2", and not "IFN?" as suggested by the Examiner. In addition, there is no horizontal code in Figure 4, and Figure 11 indicates the effect of Glucocerbroside on spleen NKT cells. As mentioned above, all figures as they appear on the PAIR system are clear and free of typographical errors. In an effort to avoid any additional confusion, Applicants forward copies of the formal drawings submitted on January 28, 2004 and May 26, 2006, as well as documentation supporting receipt by the U.S. Patent and Trademark Office. Withdrawal of the objection is respectfully requested.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are rejected under 35 U.S.C. §112, first paragraph as failing to satisfy the enablement requirement. The Examiner states that while the specification is enabling for modulation of an immune response related to hepatitis, it is not enabling for treatment of any disease associated with an inflammatory response. Office Action page 3-4. Applicants respectfully traverse the rejection.

Nature of the Invention. The Examiner states that the invention is drawn to a method for the treatment of a disease wherein there is an inflammatory immune response, comprising administering to a mammalian subject an intermediary metabolite. Office Action page 4.

State of the Prior Art. The Examiner sites to Makowska *et al.* (2000), Scan. J. Innumol. 52:71-79 (hereinafter "Makowska") as support that the prior art teaches differences in ligand specificity between NKT cells when using multiple ceramides (including glucocerebroside or glucosylceramide). The Examiner also contends that Makowska teaches αGalCer and other glycolipid variants stimulate V α14+ NKT cells. Office Action page 4. Applicants respectfully suggest that this is an improper characterization of the reference. To the contrary, Makowska showed essentially no responses with the use of βGalCer (see Tables 3 and 4). This teaches away from the use of βGalCer and calls into question the legitimacy of comparing the putative mechanisms of αGalCer versus the effects of βGalCer. Furthermore, the results shown in Makowska would not be a prediction of the positive results obtained in the experiments described in Applicants' disclosure.

Breadth of the Claims. The Examiner states that the claims cover the treatment of any and all diseases in which an inflammatory response is associated. In response to previous remarks, the Examiner has invited Applicants to provide references which teach that many diseases do not involve an inflammatory response. Office Action page 4.

Applicants respectfully disagree with the Examiner's characterization of the claim scope. Contrary to the Examiner's assertion on page 4 of the Office Action, the claims do not simply describe "any kind disease associated with inflammatory responses." Instead, the claims recite that the diseases are limited to those "wherein an inflammatory response contributes to the pathogenesis of said disease". Thus, while the Office Action on page 4 emphasizes the phrase "since many diseases do not involve inflammatory responses" from the previous response, the latter section of this quote should be emphasized as well: "for most diseases that do involve an inflammatory response this process is part of the curative process rather than the pathogenesis". The current claim language does not encompass diseases that lack an immune response, but rather diseases that exhibit an immune response and this immune response is part of the manifestation of the disease. Furthermore, it is a mischaracterization to describe the present invention as "limiting the claims to a disease

associated with an inflammatory response" (page 4 of the Office Action) since this ignores an essential limitation of the claim (as discussed above).

Applicants assert that the statement "not all diseases invoke inflammatory responses" is accurate. The Office Action states that inflammatory responses are implicit in any and all diseases ("it is absolutely untrue that many diseases do not involve an inflammatory response", Office Action page 7, emphasis added) and then asks Applicants to suggest diseases that violate this presumption. Since it would be extremely laborious to compile a complete list of any and all diseases that do not involve inflammatory responses (or at least those not known to involve such responses), Applicants cite the following examples of such diseases: hemophilia, epilepsy, acid reflux, high blood pressure, gall stones, gout, cataracts, hearing loss, congenital heart disease, cardiac arrhythmia, Bell's Palsy, sickle cell anemia, Cushing's syndrome, Lesch-Nyhan syndrome, Parkinon's disease, end-stage renal disease, gynecomastia, genetic diseases such as beta-thalasemia, coproporphyria, phenylketonuria (PKU), Duchenne's dystrophy, Huntington's chorea, polycystic kidney disease, and Kleinfelter's syndrome. If these are insufficient, additional diseases can be added as needed. However, this listing should be sufficient to demonstrate a non-obligatory connection between diseases and immune responses.

Moreover, the second part of the Applicants' statement was ignored regarding the usual beneficial aspects of immune responses for most diseases. In most cases the generation of an immune response provides a beneficial effect that either eliminates symptoms or progression of the disease state. An example of this is the response to a bacterial infection. Although a fever may develop that might produce discomfort, the development of antibodies to bacterial antigens is usually a benign process that eliminates the infection and possibly prevents its reoccurrence at a later date. In contrast, the present claims are related to a subset of diseases that **do** have immune responses, but are characterized by the induction of immune responses that are part of the pathogenesis of the disease. That is, only diseases where a defect in the immune response is part of the generation of symptoms or the progression of the disease are a subject of the present claims. As such, the nature of the diseases encompassed by the present claims are not those that are simply "associated" with an immune response, but those diseases where the immune response is part of the disease process rather than the disease cure.

Some diseases will depend upon context or differential etiology. For example,

hypothyroidism can be immune unrelated when it is derived from either an excess or lack of iodine, while the form of hypothyroidism derived from Hashimoto's thyroiditis is considered to be an autoimmune disease. In a similar fashion, adrenocortical insufficiency disease may result from Congenital Adrenal Hyperplasia, *i.e.*, a genetic defect, or it may be a presentation of Addison's disease which is usually derived from an autoimmune response destroying the adrenal cortex. (The bifurcation of the effects of the above diseases are discussed in "Cecil Essentials of Medicine" Andreoli *et al.*, editors W.B. Saunders Co. 1996, pages 456 and 462, respectively.)

Working Examples. The Examiner states that the working examples are directed towards glucocerebroside treatment of Con A induced hepatitis model, a colitis model and a model for non-alcoholic steatohepatitis, but provide no parallel to inflammatory responses for all possible diseases. The Examiner states that Applicants must point to portions of the specification which teach that the differential diseases share a common feature of an inflammatory process. Office Action page 5.

The Examiner invites Applicants to provide support for "a common feature which was described in the previous Response as 'an inflammatory process responsible for the symptoms of the disease'". Office Action page 5. The section labeled "Field of the Invention" describes "treatment of immune mediated or immune related diseases". This phrase is subsequently used numerous times in the specification and refers to diseases where at least some of the pathogenic features were caused by the immune system responses. The present invention is a continuation-in-part of U.S. Patent Application No. 10/375,906 which was incorporated by reference and published on September 2, 2004 as 2004/0171522 ("the '522 Application"). The '522 application was also directed towards treatment of "immune mediated or immune related diseases" (see paragraphs [0001] and [0007]). Also, paragraph [0036] of the '522 Application states:

> The effect can potentially be achieved using appropriate metabolite treatment either *in vivo* or *ex vivo* for any disease or condition that has a part or all of its pathology based on immune responses of the subject. Such conditions could include HBV, HCV, HIV, and other virus infections where the pathogenesis is based on an immune mediated pathogenesis" [0036]. Specification page 5.

This portion of the specification provides support for the "inflammatory response being

responsible for the symptoms of the disease." This is a common feature in Example I (concanavalin A model for hepatitis), Example II (TNBS model for colitis) and Example III (leptin deficient model of Non-Alcoholic Steatohepatitis) as all three animal models are considered to be surrogates for diseases where the immune responses are responsible for injuries to the subjects. In each case, the administration of glucocerebroside resulted in a decrease in an inflammation response that was derived from the experimental treatment. These examples are evidence of success in treating three different diseases by a single common treatment. These diseases were induced by different means and included at least two different targets: liver in the Con A model, and intestines for the TNBS model; NASH displays a variety of symptoms including diabetes and fatty liver. Therefore, as a result of this success with a plurality of disease systems , it is likely that there would be success when applied to other diseases that share a disease manifestation derived from an immune response. Furthermore, if a researcher studying a particular immune mediated disease wished to apply the present invention to a disease or a disease model other than the ones used in the examples, it would not require an inordinate amount of experimentation to either achieve success or determine that the invention was not appropriate.

Guidance in the specification. The Examiner states that the specification provides little guidance regarding the practice of the claimed methods. The Examiner further states that "something must be known to claim the treatment of all diseases with an inflammatory response and the specification lacks disclosing it." Office Action page 5.

The Examiner states that "It is not clear what the Applicants are arguing. Applicants state it is not a requirement for the practice of the invention that all parameters be known for all diseases". This phrase was a response by Applicants to a position taken by the Examiner in the previous Office Action: "Applicants fail to demonstrate that all standard parameters for all diseases are indeed known...". Applicants were disagreeing with what they perceived to be an extreme position of "all parameters" and "all diseases". Firstly, Applicants assert that a skilled practitioner who wishes to apply the present invention to a particular disease would possesses the knowledge that the disease has been recognized in the art as having an immune response contributing to the pathogenesis. As such, it would be appropriate to apply the methods of the present invention. Secondly, if the disease of interest has already been acknowledged as being an immune mediated disease, information on the parameters that were tested and used to establish the disease as being immune mediated

would be available. Therefore, the skilled practitioner already has sufficient knowledge of appropriate parameters that may be used to evaluate the successful application of the present invention. Thus, the particular parameters that would be useful in testing the effects on diseases that were not included in the examples would be known and understood by a practitioner with skill in the art.

Predictability of the art. The Examiner states that there is no predictability in the art. Office Action page 6.

The Examiner appears to be ignoring a certain level of success that has already been achieved. As mentioned before, the present application is a continuation-in-part of U.S. Patent Application No. 10/375,906. That particular disclosure was derived from observations of the effects in patients with Gaucher's Disease that were infected with HCV. At the time of the filing it was predicted that administration of an intermediary metabolite such as β-glucosylceramide should be useful in decreasing harmful immunological effects in diseases where the immune response was part of the pathogenic process. The present disclosure is an extension of that prediction. Here, as noted above, testing in three different model systems (whose only point of connection is the pathogenic aspect of the immune system in the disease process) validated this prediction and illustrates that the concepts described in the original application could be applied to multiple immune-mediated diseases. Thus, Applicants have successfully provided evidence that these concepts should be applicable to numerous diseases of such nature. It should be noted that Applicants have never designated differential cytokine response as a common factor. Instead, Applicants have explicitly stated that the common factor in diseases that are the subject of the pending claims is the involvement of the immune response in causation of the pathology of the disease.

Amount of experimentation necessary. The Examiner states that it would require years of further research to develop effect therapy for all diseases with an inflammatory response. The Examiner further states that the specification does not disclose any common feature among any disease that was successfully treated. The Examiner then concludes that it is "absolutely untrue that many diseases do not involve an inflammatory response". Office Action page 6-7.

Applicants again reiterate for emphasis that the subject of the pending claims are not "diseases with an inflammatory response" (as stated on page 7 of the Office Action) which would encompass a number of diseases that would likely not benefit from application

of the present invention. Thus, a disease where the inflammatory response is part of the pathogenesis of the disease describes only a selected subset of diseases. This lack of accordance of the Office Action with the group of diseases actually claimed can be seen by the inclusion of diseases such as cancer, pelvic inflammatory disease, and many periodontal diseases in the remarks on page 7 of the Office Action. In each of these diseases there may be inflammatory responses present but they are not part of the pathogenesis of the disease and as such, they are not covered by the pending claims. In these three diseases, there is no induction of an immune response that generates or exacerbates the symptoms of the disease and they may be more properly characterized as lacking in an adequate immune response and thereby requiring a modality to supplement the immune response.

In conclusion, claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 clearly satisfy the enablement requirement. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102(b)

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 97, 109, 119, 120, 124-126, 151, 157, 161-168, and 184 are rejected under 35 U.S.C. §102(b) as being anticipated by Liotta *et al.* (U.S. Patent No. 6,610,835, hereinafter "Liotta"). The Examiner states that Liotta describes the use of sphingolipid derivatives and their methods of use, including the treatment of inflammatory conditions. The Examiner further states that the compounds used in Liotta are suited for the treatment of colitis. The Examiner then states that "The authors provide the same method steps comprising administering the same ingredient to the same population. Inherently, this would result in the same effects, including changes in cytokine responses, NKT cells or Th1/Th2 balance". Office Action page 8.

To support a rejection under Section 102, an Examiner must show that each and every element recited in the claimed invention is taught by a single reference. MPEP § 2131. The Examiner describes the teachings of Liotta with phrases such as "the use of sphingolipid derivatives", "sphingolipid conjugates" and "terminally polar sphingolipids". Office Action page 8. Furthermore, the Liotta specification reads:

> ...it would be of benefit to provide new sphingolipid derivatives that improved properties, bioavailability, or are targeted to desired locations for effective therapy. It is therefore an object of the present invention to provide new sphingolipids ....column 8 lines 16-21.

The above language clearly illustrates that Liotta has no teaching of administration of mammalian intermediary metabolites, even in the form of sphingolipids. To the contrary, Liotta teaches only that such natural forms of sphingolipids are inadequate. Liotta discloses the use sphingolipid derivatives, *i.e.* artificial analogues of the natural sphingolipids found in mammalian cells. The compositions taught by Liotta are not identical or substantially identical to natural mammalian sphingolipids. Therefore, Liotta dose not teach each and every element of the present claims. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §103(a)

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are rejected under 35 U.S.C. §103(a) as being obvious over Liotta, Makowska and Tanguchi *et al.* (EP 0988860; hereinafter "Tanguchi"). The Examiner states that while Liotta dos not teach the use of CD1 receptor presenting cells, glucosylceramide or galactosylceramide, or food depravation, Liotta does teach that sphingolipids are found in a number of foods. The Examiner then concludes that the invention as a whole is obvious. Office Action page 10. The Examiner then states that Makowska demonstrates the use of alpha-glucosylceramide in stimulating NKT cells (Vα14+). The Examiner then writes that Tanguchi teaches a method of treating disorders (including ulcerative colitis) through the use of glycosylceramides and derivatives for the activation of NKT cells. The Examiner then concludes that it would have been obvious to combine the teachings of Makowska and Tanguchi to perform a method of administering an intermediary metabolite with an antigen presenting cell. Office Action page 10-11.

Applicants respectfully traverse the rejection. The recently revised Examiner guidelines for assessing obviousness set forth detailed requirements based on asserted rationales for obviousness. The Rationales To Support Rejections Under 35 U.S.C. §103 provide the following possible rationales:

> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;

> (C) Use of known technique to improve similar devices (methods or products) in the same way;
>
> (D) Applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
>
> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

See MPEP 8th Edition, rev. 6, §2141.

Applicants proceed with the understanding that this rejection conforms to rationale G quoted above. The MPEP further sets forth the requirements for an obviousness rejection under this rationale:

> To reject a claim based on [rationale G], Office personnel must resolve the Graham factual inquiries. Then, Office personnel must articulate the following:
>
> (1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
>
> (2) a finding that there was reasonable expectation of success; and
>
> (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
>
> The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). **If any of these findings**

> **cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.** [emphasis added]

See MPEP 8th Edition, rev 6, §2143

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. See MPEP 8th Edition, rev 6, § 2143.

Applicants respectfully traverse the rejection. As explained above, Liotta neither teaches nor discloses administration of mammalian intermediary metabolites. Liotta teaches analogues rather than natural products. This deficiency is not remedied by Tanguchi. Neither of these references would suggest that the natural glucosylceramides would be effective. As previously mentioned, Makowska teaches away from the use of natural glucosylceramides by an observation of complete ineffectiveness of β-glycosylceramides compared to the α-analogues. Contrary to the Examiners assertion on page 11 of the Office Action, the combination of the references provides no teaching of administration of an intermediary metabolite (with or without an antigen presenting cells). None of the references encourages the use of a normal mammalian intermediary metabolite, but instead only encourages the use of non-natural products which would not normally be found within a mammalian cell. A person of skill in the art would have no motivation to combine references because the combination does not result in Applicants presently claimed invention. There would be no expectation that the combination would be successful because references that describe and support the use of α-glucocerebroside (*i.e.*, those cited by the Examiner) teach away from the use of β-glucocerebroside.

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 76, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are not rendered obvious by the combination of Liotta, Makowska and Tanguchi. Applicants respectfully request withdrawal of the rejection.

Double Patenting

Claims 1, 6, 11, 43-45, 47-52, 54, 59, 60, 75, 97, 109, 119, 120, 124-126, 151, 157, 161-170, 184, 191, and 205 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 9-15 of copending Application No. 11/378,941.

As this is a provisional rejection, Applicants respectfully request the rejection be held in abeyance until the finding of allowable subject matter.

Conclusion

Applicants respectfully submit that all claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

THE WEBB LAW FIRM

By Kellie L. Carden

Kellie L. Carden
Registration No. 52,696
Attorney for Applicants
436 Seventh Avenue
700 Koppers Building
Pittsburgh, PA 15219
Telephone: (412) 471-8815
Facsimile: (412) 471-4094
E-mail: webblaw@webblaw.com